REMARKS

In response to the Official Action mailed August 9, 2010, reconsideration of the pending claims is respectfully requested. No claims have been amended or cancelled by this response. Reconsideration of the pending claims in view of the below remarks is respectfully requested.

Claims 1-9, 13-32, directed to the following species: 1) BCG and interferon γ, or LPS, TNFα as maturing agents, and 2) CD86 or CD80 co-stimulatory molecule have been examined in the instant application. All remarks in the present response are directed to the currently elected species although certain claims have not been amended to cancel the non-elected subject matter. Should the generic claims be found allowable, Applicant respectfully requests rejoinder of a reasonable number of non-elected species as set forth in M.P.E.P. § 821.04.

Rejections Under 35 U.S.C. § 102:

Claims 1-3, 5, and 13 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Triozzi *et al.* and as evidenced by Labeur *et al.* for the reasons of record. The Examiner has considered Applicant's prior arguments and has not found them to be persuasive. In particular, the Examiner has remarked that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. Further, the Examiner alleges that the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi *et al.* are reasonably interpreted as partially matured dendritic cells because the language "partially matured dendritic cells" is a relative term, and because Labeur *et al.* teach that murine DCs treated in GM-CSF and IL-4 have an intermediate degree of maturation between bone marrow cells cultured in GM-CSF alone and the more mature DCs treated with GM-CSF and IL-4 plus LPS or CD40L, and also murine DCs treated with GM-CSF and IL-4 have the ability to take up and process antigen, present antigen, and stimulate T cells. The Examiner has also alleged that Applicant's prior response does not have any objective evidence or references showing that induction of an intermediate maturity of dendritic cells from murine bone marrow by GM-CSF, as taught by

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Labeur *et al.*, would not apply to dendritic cells from murine or human monocytes. Still further, the Examiner has dismissed Applicant's remarks describing the Examples in the present application showing that murine bone marrow cells cultured in the presence of GM-CSF and IL-4 differ in their ability to take up and process tumor antigens when compared with murine bone marrow cells partially matured by contact with BCG and IFNγ by asserting that the limitation of BCG and IFNγ is not in claims 1-3, 5, and 13.

The Examiner further asserts that although Triozzi *et al.* do not explicitly name the dendritic cells treated with GM-CSF and IL-4 as partially matured dendritic cells, the claimed partially matured dendritic cells appear to be the same as the prior art dendritic cells. As such, the Examiner believes that in the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed product is different from that taught by the prior art and to establish patentable differences.

Applicant again does not agree with the rejection of the Examiner, the method taught by Triozzi *et al.* does not use partially mature dendritic cells and Labeur *et al.* does not support the Examiner's allegation that they are. The method of Triozzi *et al.* contacts monocytic dendritic cell precursors with the dendritic cell differentiation agents GM-CSF and IL-4. It is well known to the skilled artisan that the cells obtained by this method are immature dendritic cells. As previously submitted, monocytes contacted with GM-CSF and IL-4 differentiate into immature dendritic cells as evidenced by Sallusto and Lanzavecchia. To the contrary, Labeur *et al.* teach that hematopoietic stem cells (HSCs) contacted with GM-CSF differ in certain characteristics from HSCs contacted with GM-CSF and IL-4 and with HSCs contacted with GM-CSF, IL-4 and Flt3. It is well known to an artisan of ordinary skill in the antigen presenting cell/dendritic cell art that there are differences in the differentiation and maturation pathways for HSC dendritic cell precursors and for peripheral blood monocyte dendritic cell precursors. In particular, it is well known that HSCs and monocytes are induced to differentiate with different cytokines and culture conditions. As such, the teachings of Labeur *et al.* regarding the differentiation/maturation of HSC dendritic cell precursors can not be used to characterize the

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differentiation status or maturation status of the monocytic dendritic cell precursors used by Triozzi *et al.* The work of Sallusto and Lanzavecchia, and others clearly support Applicant's position that the cells administered by Triozzi *et al.* are not the same as the partially matured dendritic cells of the present claims.

Applicant respectfully requests the Examiner reconsider the rejection of claims 1-3, 5 and 13 under 35 U.S.C. § 102(a) as being anticipated by Triozzi *et al.* as evidenced by Labeur *et al.*

Rejections under 35 U.S.C. § 103:

Claims 2 and 4 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.* in view of Labeur *et al.* and further in view of Murphy *et al.* for the reasons already of record. The Examiner has considered Applicant's prior response and has found it to be unpersuasive. In particular, the Examiner alleges that the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi *et al.*, and as evidenced by Labeur *et al.* appear to be the same as the claimed partially matured dendritic cells for the reasons as set forth above. Further, the Examiner has alleged that it would be *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to obtain the dendritic cells taught by Triozzi *et al.* and Labeur *et al.* from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood, as taught by Murphy *et al.* to increase the number of available sources for making dendritic cells. It is also the belief of the Examiner that it would have been obvious to replace dendritic cells obtained from the individual to be treated, taught by Triozzi *et al.* and Labeur *et al.* with dendritic cells from a healthy individual HLA-matched to the individual to be treated as taught by Murphy *et al.* to increase the number of available dendritic cells, for example, in situations where the patient to be treated cannot provide sufficient dendritic cells, as taught by Murphy *et al.* Still further, the Examiner has alleged that an HLA-matched dendritic cell would be necessary, because antigen presentation of dendritic cells is restricted to the complementing HLA molecule, in view of the teachings of Murphy *et al.*

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Applicant must again strongly disagree with this rejection. As above, the immature dendritic cells administered by Triozzi *et al.* are clearly not the same as the partially mature dendritic cells of the pending claims. One of skill in the art recognizes that the methods for obtaining immature and/or mature dendritic cells from hematopoietic stem cells (HSCs) are very different from the methods for obtaining immature and/or mature dendritic cells from peripheral blood monocytes, or from other dendritic cell precursors. As such, the teachings of Labeur *et al.* can not be used to determine the differentiation status or maturation status of the cells administered by Triozzi *et al.* The work of Sallusto and Lanzavecchia, previously submitted, and others clearly demonstrates that the cells of Triozzi *et al.* would be considered by the artisan of ordinary skill to be immature dendritic cells and not partially mature dendritic cells as recited in the claims of the present application.

The addition of Murphy *et al.* does nothing to provide the elements missing from Triozzi *et al.* and/or Labeur *et al.* when considered either alone or in any combination. Therefore, as the Examiner has failed to establish a *prima facie* case for obviousness, Applicant respectfully request that the Examiner reconsider and withdraw the rejections of claims 2 and 4 as being obvious and unpatentable over Triozzi *et al.* in view of Labeur *et al.*, and further in view of Murphy *et al.*

Claims 6-9 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, in view of Labeur *et al.*, and further in view of US 2005 0059151 (Bosch *et al.*) and Chakraborty *et al.*, for the reasons already of record. The Examiner has considered Applicant's prior response and considers the response unpersuasive. In particular, the Examiner alleges, as above, that the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi *et al.* appear to be the same as the presently recited partially matured dendritic cells in the pending claims of this application. Further, the Examiner believes that although Bosch *et al.* use treated dendritic cells that have been exposed to antigen prior to their administration to a subject, the primary reference, Triozzi *et al.* teach the use of treated dendritic cells for administration to a cancer patient, without the need of their exposure to a cancer antigen, prior to their administration to the patient. As such, the Examiner believes that it would have been *prima facie* obvious for one of

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ordinary skill in the art at the time the invention was made to add to GM-CSF plus IL-4 maturing agent taught by Triozzi *et al.* and Labeur *et al.* with BCG and interferon γ, as taught by Bosch *et al.* in the method taught by Triozzi *et al.* and Labeur *et al.* for maturing dendritic cells *in vitro* for use in producing an anti-cancer response, because the use of BCG and interferon γ as maturation agents as taught by Bosch *et al.* would be advantageous, in view of the fact that they selectively enhance the production of stimulating dendritic cells that secrete IL-12, and therefore, efficiently stimulate T cells, in view of the teachings of Chakraborty *et al.*, and promoting anti-tumor immunity, in view of the teachings of Labeur *et al.*

Applicant again must respectfully disagree with the rejection of the Examiner. As above, Labeur *et al.* do not teach or suggest the differentiation status or maturation status of the cells obtained by the methods of Triozzi *et al.* The skilled artisan of ordinary skill in the antigen presenting cell/dendritic cell art knows well that the methods used to induce the differentiation of hematopoietic stem cell dendritic cell precursors are different from the methods for differentiating an/or maturing peripheral blood monocytic dendritic cell precursors. As such, the characterization of the cells obtained by Labeur *et al.* does not provide the skilled artisan with any information regarding the status of the cells obtained by and administered to patients by Triozzi *et al.* Further, Bosch *et al.* and/or Chakraborty *et al.* when considered either alone or in any combination do not disclose or suggest any element missing for the teachings of Labeur *et al.* and/or Triozzi *et al.* that would render obvious claims 6-9. Therefore, the Examiner has not set forth a *prima facie* case for obviousness, Applicant respectfully requests that the Examiner reconsider and withdraw the present rejection of claims 6-9 as being obvious over Triozzi *et al.*, in view of Labeur *et al.*, and further in view of Bosch *et al.* and Chakraborty *et al.*

Claims 14-18 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, in view of Labeur *et al.*, for the reasons already of record. The Examiner has considered Applicant's prior response and found it to be non-persuasive. In particular, as above, the Examiner believes that the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi *et al.*, and as evidenced by Labeur *et al.* appear to be the same as the claimed partially matured dendritic cells, as set forth above. Further, the Examiner alleges that it would have been obvious

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to one of ordinary skill in the art to choose direct administration of the partially matured dendritic cells taught by Triozzi *et al.*, as evidenced by Labeur *et al.*, over subcutaneous injection, because dendritic cells migrate inefficiently into the regional lymph nodes after subcutaneous injection into mice, as taught by Labeur *et al.*

Applicant again must respectfully disagree with the rejection of the Examiner. As above, Triozzi *et al.* teach the administration of immature dendritic cells that have been derived from monocytic dendritic cell precursors. Labeur *et al.* do not teach a method for differentiation and/or inducing the maturation of the same cells. As such, any characterization of the cells obtained by Labeur *et al.* does not inform the skilled artisan as to the status of the cells obtained using the methods of Triozzi *et al.* References such as Sallusto and Lanzavecchia, previously cited, teach that the cells of Triozzi *et al.* are immature dendritic cells and not partially mature dendritic cells as used in the pending claims of the instant application. As such, it would not be obvious to one of skill in the art to choose direct administration of partially mature dendritic cells over subcutaneous injections for any reason.

In view of the above remarks, the Examiner is respectfully requested to reconsider and withdraw the rejections of claims 14-18 as being unpatentable under 35 U.S.C. § 103(a) over Triozzi *et al.* in view of Labeur *et al.*

Claims 19 and 20 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, in view of Labeur *et al.*, and further in view of Nikitina *et al.*, for the reasons already of record. The Examiner has considered the prior response of Applicant's and found it to be non-persuasive. In particular, the Examiner, as above, believes that the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi *et al.*, and as evidenced by Labeur *et al.* appear to be the same as the claimed partially matured dendritic cells. Further, the Examiner believes that it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to combine dendritic cells taught by Triozzi *et al.* and Labeur *et al.* with radiation therapy, because gamma radiation induces the dramatic ability of dendritic cells injected

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intravenously or subcutaneously. to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response, as taught by Nikitina *et al.*

Again as above, Applicant must again respectfully disagree with the rejection of claims 19 and 20 as being obvious over Triozzi *et al.* in view of Labeur *et al.*, and further in view of Nikitina *et al.* Triozzi *et al.* do not teach methods for the administration of partially mature dendritic cells, but instead are clearly directed to methods for administration of immature dendritic cells. Labeur *et al.* does not provide any information to the artisan of ordinary skill in the art to change the characterization of the cells obtained by Triozzi *et al.* Sallusto and Lanzavecchia clearly teach that the cells obtained by the methods of Triozzi *et al.* are immature dendritic cells and are not the same as those recited in the pending claims. Nikitina *et al.* fails to add any element to the combination of Triozzi *et al.* and Labeur *et al.* that would result in the methods of the present claims 19 and 20. As such, Applicant respectfully requests the Examiner reconsider and withdraw the present rejection of claims 19 and 20.

Claims 21-23, 25, and 27-32 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, in view of Labeur *et al.* and Sukhatme *et al.*, for the reasons of record. The Examiner has considered Applicant's prior response and has found the response to be unpersuasive. In particular, the Examiner believes that the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi *et al.*, and as evidenced by Labeur *et al.* appear to be the same as the claimed partially matured dendritic cells. Further, the Examiner believes dendritic cells generated *in vitro* by GM-CSF and IL-4 taught by the art express the same elected co-stimulatory molecules CD80 and CD86 as claimed in claim 22. In addition, the Examiner has noted that the other indicators described in the response, such as, CD11c, CD14, the phosphorylation level of a number of intracellular proteins, including jak2, the amounts of IL-10 and/orIL-12, the down

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regulation of cytokine receptors on the cell surface, are not recited in the claims, and therefore the arguments are moot.

Applicant must again respectfully disagree with the rejections of claims 21-23, 25, and 27-32. In particular, the dendritic cells obtained by the culture of monocytic dendritic cell precursors in the presence of GM-CSF and IL-4 taught by Triozzi *et al.* are clearly not the same as the dendritic cells taught by Labeur *et al.* The cells taught by Triozzi *et al.* are well known to the skilled artisan to be immature dendritic cells, as taught by Sallusto and Lanzavecchia, and not partially mature dendritic cells as taught in the present application. While the Examiner may be correct that the CD80 and CD86 co-stimulatory molecules shown by Triozzi *et al.* to be on certain cells obtained by the disclosed methods are the same as those recited in claim 22, the dendritic cells are not partially matured and the amount of each co-stimulatory molecule, CD80 and CD86, is increased by the *in vitro* induction of maturation to form the partially mature dendritic cells of the present invention. As the immature dendritic cells taught by Triozzi *et al.* are not the same as the partially mature dendritic cells recited in the claims of the present application, the presence of absence of the CD80 and/or CD86 co-stimulatory molecules is moot. Further, Sukhatme *et al.* does not teach the elements missing from Triozzi *et al.* and/or Labeur *et al.* when consider either alone or in combination. As such, the Examiner has not presented a *prima facie* case for obviousness.

Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 21-23, 25, and 27-32 under 35 U.S.C. § 103(a) as being unpatentable

Claim 26 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, in view of Labeur *et al.*, and Murphy *et al.*, for the reasons already of record. The Examiner has consider Applicant's prior response and did not find the reasoning persuasive. In particular,

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the Examiner, as above, believes that the dendritic cells treated with GM-CSF and IL-4 taught by Triozzi *et al.* and as evidenced by Labeur *et al.* appear to be the same as the claimed partially mature dendritic cells. Further, the Examiner believes that it would have been obvious that to replace dendritic cells from the individual to be treated taught by Triozzi *et al.* and Labeur *et al.* with dendritic cells that have been isolated from a healthy individual, HLA-matched to the individual to be treated, as taught by Murphy *et al.* to increase the number of available dendritic cells. Still further, the Examiner alleges that an HLA-matched dendritic cell would be necessary because antigen presentation of dendritic cells is restricted to the complementing HLA molecule, in view of the teachings of Murphy *et al.*

Applicant again must respectfully disagree with the rejection of claim 26 as being unpatentable. As above, the immature dendritic cells of Triozzi *et al.* are not the same as the dendritic cells of Labeur *et al.* It is well known to the skilled artisan that the methods for the differentiation and/or maturation of monocytic dendritic cell precursors are not the same as the methods for the differentiation and/or maturation of dendritic cells from hematopoietic stem cells. Given that the cells of Triozzi *et al.* are immature dendritic cells and not partially mature dendritic cells it would not have been obvious to replace the dendritic cells for the individual to be treated taught by Triozzi *et al.* and Labeur *et al.* with dendritic cells isolated from a healthy individual HLA matched to the individual to be treated, as taught by Murphy *et al.*

Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claim 26 as being unpatentable under 35 U.S.C. § 103(a) over Triozzi *et al.*, in view of Labeur *et al.*, and further in view of Murphy *et al.* in view of the above remarks.

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Rejections under 35 U.S.C. § 112:

Claims 1-9, and 13-32 are newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regard as the invention. In particular, the Examiner alleges that the term "partially mature" in claims 1-9, and 13-32 is a relative term which renders the claim indefinite. Further, the Examiner alleges that the term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the claim.

Applicant disagrees with the rejection of the Examiner that the term "partially matured" as used in Claims 1-9 and 13-32 is indefinite for failing to particularly point out and distinctly claim the subject matter which is regarded as the invention. The Examiner has alleged that the claims do not define the term "partially mature" and that the specification does not provide a standard by which the skilled artisan can determine the scope of the claim. Applicant believes that the term is sufficiently definite that one of ordinary skill in the art is reasonably apprised of the scope of the invention. Dendritic cells when examined *in vitro* are typically characterized in the art as being immature or mature. Immature dendritic cells have a set of characteristics that are understood by the artisan of ordinary skill to include expression of certain surface marker, the ability to take up and process soluble antigen, and to have a limited ability to stimulate T cell proliferation. Mature dendritic cells are known to the skilled artisan to have increased expression of certain co-stimulatory molecules, such as CD54, CD80 and CD86, when compared to immature dendritic cells, they no longer take up and process substantial amounts of antigen, and they have increased ability to stimulate T cell proliferation. Dendritic cells that have been partially matured *n vitro* would be known to the skilled artisan to have characteristics between

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immature dendritic cells and mature dendritic cells. The present inventors have been able to show an increased ability of dendritic cells that have been induced to begin maturation from immature dendritic cells to maintain an immune response against a tumor when administered to an individual. Further, the specification provides a means to compare and distinguish a partially mature dendritic cell from one that is fully mature and the claim recites that the dendritic cell must be induced to mature *in vitro* to be considered partially mature. Given these requirements, one of skill in the art has a more than reasonable standard to determine the scope of the claims. As such, Applicant believe that the term "partially mature" is definite and meets the requirements of 35 U.S.C. § 112, second paragraph.

Applicant respectfully requests the Examiner reconsider and withdraw the rejection of Claims 1-9, and 13-32 under 35. U.S.C. § 112, second paragraph as being indefinite in view of the above remarks.

Respectfully submitted,

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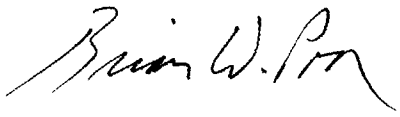

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